III. REMARKS/ARGUMENTS

A. Status of Claims

Claims 38 and 47-56 are currently pending. Claims 1-37 and 39-46 were previously cancelled. Claim 38 has been amended herein without prejudice. It is respectfully submitted that no new matter has been added by virtue of this amendment.

B. 35 U.S.C. §103 Rejection of Claims 38, 47-48 and 50-52 Based Upon U.S. Patent No. 4,569,937 to Baker et al.; Friedel et al. (Drugs, 1993. Vol. 45(1), pp. 131-156); and Eversmeyer et al. (American Journal of Medicine, Aug. 1993, Vol. 95, pp. 10S-18S).

Applicants respectfully submit that the combination of the Baker reference, the Friedel reference and the Eversmeyer reference fail to teach or suggest the presently claimed method of effectively treating pain by administering a combination of two analgesic compounds or pharmaceutically acceptable salts thereof consisting of (i) nabumetone and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof.

a. There is no motivation to substitute the ibuprofen in the synergistic combination of the Baker composition with another NSAID

Applicants respectfully submit that the combination of the Baker, Friedel and Eversmeyer references fail to provide the motivation to one of ordinary skill in the art to substitute the ibuprofen in the Baker formulation with any other NSAID, let alone nabumetone, as discussed in the Friedel and Eversmeyer references.

The Baker reference teaches a synergistic combination of narcotic analgesics and ibuprofen. It appears that the Examiner is overlooking the fact that the Baker reference utilizes ibuprofen because of its enhanced analgesic effect it has with

oxycodone. There is nothing in the Friedel and Eversmeyer references to suggest that nabumetone would have this effect also, therefore there is no motivation to substitute the ibuprofen in the Baker composition with nabumetone. Applicants respectfully point out that the purported invention of the Baker reference is directed to pharmaceutical compositions of narcotic analgesics and ibuprofen which "... exhibit unexpectedly enhanced analgesic activity ..." (See Abstract). The Baker reference is therefore limited to combinations wherein the NSAID is ibuprofen and does not teach or suggest that the purported "unexpectedly enhanced analgesic activity" would occur with an NSAID which is different than ibuprofen.

Applicants further submit that, in view of the above, the Baker reference teaches away from substituting ibuprofen with another NSAID (e.g., nabumetone), because of the unexpected synergy that it purports for the combination of ibuprofen with a narcotic analgesic. Accordingly, due to this purported synergy, one skilled in the art would be discouraged to combine the Baker reference with the Friedel and Eversmeyer references in order to select an NSAID different than ibuprofen (i.e., nabumetone) to combine with oxycodone. "A prior art reference may be considered to teach away when 'a person of ordinary skill, upon reading the reference would be discouraged from the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 45 USPQ2d 1977, 1984 (Fed. Cir. 1998). Therefore, Applicants submit that, as a whole, the Baker reference would steer one of ordinary skill in the art away from combining the Baker reference with the Friedel and Eversmeyer references to select an NSAID different than ibuprofen (i.e., nabumetone) to combine with oxycodone, for the reasons argued above.

In addition, Applicants submit that modifying the formulation of the Baker reference in view of Friedel and Eversmeyer references, as proposed by the Examiner, by substituting ibuprofen with nabumetone would result in a dosage form which is not directed to the principle of operation described in the Baker reference (i.e., the purported synergism of narcotic analgesics and ibuprofen). "If the proposed modification or combination of the prior art would change the principle of operation of the prior art

invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." See MPEP 8th edition, Revision 2, p.2100-132.

b. The reference to NSAIDs in the Background of the Invention in the Baker reference specifically refers to the limited compounds in the Sunshine reference which do not include nabumetone

In the August 1, 2006 Final Office Action, the Examiner stated that "Baker teaches the advantages such as enhanced analgesic effect by combining narcotic analgesics and NSAID in general", and cited to the Baker reference at column 1, lines 21+. The Examiner further stated that the Baker reference teaches "the class of drugs that are known as NSAID...", and cited the Baker reference at Col. 1-2.

Applicants respectfully point out that column 2 of the Baker reference makes no mention of the term "NSAID". Applicants further point out that the relevant portion of column 1 of the Baker reference states that "[t]his patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone." The phrase "this patent" actually refers to U.S. Patent No. 4,464,376 issued to A. Sunshine et al. (hereinafter "the Sunshine reference"). The two references to the term "NSAID" at column 1, lines 17-27, are the only recitations of the term "NSAID" in the entire patent, and they are with reference to the teachings of the Sunshine reference.

In the November 28, 2006 Advisory Action, the Examiner stated that "the obviousness rejection as set forth in the previous Office action is based on the combination of the Baker, Friedel and Eversmeyer references, not a combination of Baker and Sunshine. The Sunshine reference only offers examples of prior art's teaching". Applicants respectfully point out that all of the reference to NSAIDs in the Baker reference, as cited by the Examiner, only relate to the teachings of the Sunshine reference. Therefore, one of ordinary skill in the art would necessarily look to the disclosure of the Sunshine reference to interpret the meaning and use of NSAIDs as

discussed in the Baker reference. It is only proper to look to the Sunshine reference for the context in which NSAIDs are described in the Baker reference.

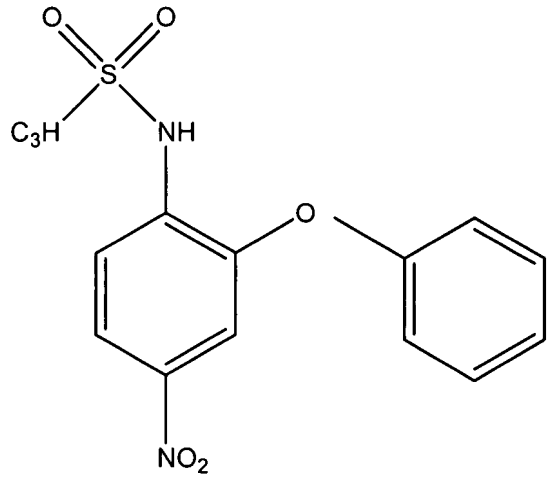
To that end, Applicants respectfully point out that the purported invention in the Sunshine reference is directed to combinations of caffeine and NSAIDs; caffeine and narcotic analgesics; and caffeine and NSAIDs/narcotic analgesics. Therefore, the summation that "the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone" is in reference to a combination of three active components, i.e. NSAIDs, narcotic analgesics and caffeine, not the ibuprofen/narcotic analgesic combination of the Baker reference.

Furthermore, Applicants point to the Sunshine reference at column 14, lines 58-61, which recite "[t]he term 'selected NSAID' as used herein is intended to mean any non-narcotic analgesic/nonsteroidal anti-inflammatory compound **falling within one of the five structural categories indicated hereinabove**." (Emphasis added).

These five categories are set forth at column 7, lines 42-50 of the Sunshine reference which states that:

> The non-narcotic analgesics/nonsteroidal anti-inflammatory drugs for use in the compositions and methods of the present invention can be selected from the following categories:
> (1) the propionic acid derivatives;
> (2) the acetic acid derivatives;
> (3) the fenamic acid derivatives;
> (4) the biphenylcarboxylic acid derivatives; and
> (5) the oxicams.

The chemical structures of the (5) categories are exemplified in columns 8-11. Applicants submit that the chemical structure of the presently claimed NSAID, *i.e.* nabumetone:



does not fall within any of the five structural categories indicated above. Therefore, even assuming arguendo that the Baker reference contemplates the use of other NSAIDs based on the reference to the Sunshine reference, Applicants submit that the "other" NSAIDs would be limited to the five structural categories listed in Sunshine and would not include nabumetone.

Further, Applicants respectfully submit that it is improper for the Examiner to rely solely on the Background of the Invention of the Baker reference and ignore the further teaching of this reference. "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Accordingly, it is Applicants' position that when evaluated as a whole, the Baker reference teaches that ibuprofen provides a synergistic effect in combination with narcotic analgesics and therefore leads away from substituting the ibuprofen with nabumetone as suggested by the Examiner.

Therefore, it is Applicants position that the Baker reference as a whole does not teach or suggest the use of any NSAIDs other than ibuprofen, as the only mention of "NSAIDs" is in the "Background of the Invention". However, even assuming arguendo that the Baker reference teaches other NSAIDs, Applicants submit that the "other" NSAIDs would not include nabumetone as discussed above with reference to the Sunshine reference.

c. The Eversmeyer and Friedel references do not definitively conclude that nabumetone is equally efficacious with less side effects than ibuprofen

In the prosecution history of the present application, the Examiner concluded that "the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, but is safer with less side effects (e.g. as compared to ibuprofen)." October 6, 2005 Office Action. In making this conclusion, Applicants respectfully submit that the Examiner is relying on only certain portions of the Eversmeyer and Friedel references and appears to be ignoring particular portions of these references which conclude that nabumetone exhibited similar or even more of certain side-effects as compared to ibuprofen. Therefore, Applicants respectfully submit that the Examiner is not considering the prior art references as a whole and is mischaracterizing the conclusions of the studies performed in the Eversmeyer and Friedel references.

In support of this position, Applicants respectfully point out that, for example, Figure 1 of the Eversmeyer reference shows that as compared to ibuprofen, patients receiving nabumetone exhibited more dyspepsia at higher doses as compared to ibuprofen, more nausea at both lower and higher doses as compared to ibuprofen and more diarrhea at both lower and higher doses as compared to ibuprofen. Figure 3 of the Eversmeyer reference shows that patients receiving nabumetone had elevations in both SGOT and SGPT levels as compared to patients receiving ibuprofen (there were no patients receiving ibuprofen who showed elevated SGOT or SGPT levels). Additionally, Table V of the Eversmeyer reference shows that 10.7% of patients receiving nabumetone withdrew from the study, as compared to only 8.1% of patients receiving ibuprofen. Further, Table V indicates that patients receiving nabumetone exhibited more abnormal hepatic function, diarrhea, edema, flatulence, gastritis, headache and rash than patients receiving ibuprofen.

With respect to the Freidel, Applicants note that this reference refers to a study which showed that nabumetone was less efficacious than ibuprofen:

> *Jenner (1987) reviewed the results of a series of multicentre trials...in which nabumetone was administered to a total of 986 patients with skin and soft tissue injuries. The largest of these were comparative trials versus placebo, soluble aspirin, ibuprofen and naproxen...In the double blind studies...ibuprofen was superior to nabumetone in the physician-assessed degree of recovery.*
> Friedel at page 147 (Emphasis added).

Applicants further point out the following portions of Friedel which the Examiner appears to disregard:

> *"[w]hile gastrointestinal tolerability is better with nabumetone than with aspirin, slow release diclofenac and possibly naproxen and indomethacin, the overall profile of gastrointestinal symptoms is qualitatively similar to that of other NSAIDs";*
>
> *By the time of the previous review in the Journal...over 4000 patients had received nabumetone in clinical trials worldwide. The profile of adverse events which emerged from these studies was similar to that described with other NSAIDs*
>
> *[T]he incidence of gastrointestinal symptoms attributed to nabumetone was comparable with that of...ibuprofen...*
>
> *[G]astrointestinal events have occurred less frequently with nabumetone than with aspirin or slow release diclofenac, and less frequently than with naproxen and indomethacin in some, but not all studies.*
> Friedel at pages 133;148;150;153.

When viewing the Friedel and Eversmeyer references in their entireties, Applicants submit that that these references do not definitively conclude that nabumetone is equally efficacious and safer with less side effects than ibuprofen, as improperly construed by the Examiner. These references are inconclusive at best, and with respect to particular side effects, can be viewed as teaching away from the use of nabumetone in

combination with oxycodone. Therefore, Applicants submit that the references fail to provide the motivation to substitute nabumetone for the ibuprofen utilized in the Baker reference.

d. The Examiner is not considering the invention as a whole

Applicants further submit that the Examiner is focusing solely on the nabumetone component of the present invention, and not the invention as a whole, i.e., nabumetone in combination with oxycodone. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." MPEP 8th Ed. 4th Rev. § 2140.02, citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983). As discussed *supra*, the Examiner has relied upon the side-effects exhibited by patients receiving nabumetone and ibuprofen to show motivation by the Eversmeyer and Friedel references to make and use the present invention. However, the Examiner has not considered the side-effects of oxycodone. To that end, Applicants have provided as Exhibit A, page 2244 of the Physician's Desk Reference (1996), which states that "the most frequently observed adverse reactions include light headedness, dizziness, sedation, nausea and vomiting...other adverse reactions include euphoria, dysphoria, constipation, skin rash and puritis." For the Examiner's convenience, the chart below shows common side-effects of oxycodone, nabumetone and ibuprofen.[1]

Common Side Effect of Oxycodone, Nambumetone and Ibuprofen	**Nabumetone (% of patients who exhibited side-effect)**	**Ibuprofen (% of patients who exhibited side effect)**
Dizziness	0.9	1.7
Nausea	4.0	4.3
Vomiting	0.5	0.4
Constipation	1.7	0.9
Skin rash	1.3	0.9

[1] Side-effects of nabumetone and ibuprofen from Table II, page 12S of the Eversmeyer reference.

Out of the common side-effects for these three agents, three of the five side effects (i.e., vomiting, constipation and skin rash) occurred more frequently with nabumetone than with ibuprofen. Therefore, Applicants submit that the teachings of the cited references would not motivate one of skill in the art to select nabumetone over ibuprofen to combine with oxycodone, as one of skill in the art would expect that more common side-effects of oxycodone are likely to be exacerbated with nabumetone than with ibuprofen. Rather, Applicants respectfully submit that this comparative data would teach away from the use of nabumetone with oxycodone. Therefore, Applicants submit that the references fail to provide the motivation to substitute nabumetone for the ibuprofen utilized in the Baker reference.

e. The Examiner is relying on an improper "obvious to try" rationale

Applicants submit that the Examiner is applying an improper "obvious to try" rationale in suggesting the substitution of ibuprofen with nabumetone. "In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir.1988). Applicants submit that *In re O'Farrell* is analogous to the present situation, where one of ordinary skill in the art would have to try each of numerous possible NSAIDs in place of ibuprofen in order to arrive at the selection of nabumetone, as the Baker reference gives no direction as to what NSAIDs other than ibuprofen would be successful.

f. The Examiner is improperly picking and choosing ibuprofen and oxycodone from the prior art

Applicants submit that the Examiner is improperly picking and choosing the nabumetone of the Friedel and Eversmeyer references and the oxycodone of the Baker reference to recreate the claims of the present application. One "...cannot pick and

choose among the individual elements of assorted prior art references to recreate the claimed invention." *SmithKline Diagnostics, Inc. v. Helena Laboratories Corporation*, 859 F.2d 878, 887 (Fed. Cir. 1988).

Based on Applicants review of the Baker reference, it appears that the inventors in the Baker reference rejected all NSAIDs in their invention *except* ibuprofen. The purported invention and teachings of the Baker reference are limited to the combination of a narcotic analgesic and ibuprofen. For example, column 1, lines 6 - 9 of the Baker reference states as follows:

> *This invention relates to pharmaceutical compositions of narcotic analgesics and ibuprofen having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals.*
> (Emphasis Added)

Column 2, lines 11-15 of the Baker reference states as follows:

> *According to the present invention there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof,...*
> (Emphasis Added)

The following additional passages from the Baker reference are also limited to a combination of narcotic analgesics and ibuprofen:

Column/Lines	**Text**
Title:	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Abstract:	ABSTRACT Pharmaceutical compositions of narcotic analgesics and ibuprofen . . .
Figure 1	ISOBOLOGRAM FOR THE INTERACTION OF ORAL OXYCODONE HCL AND IBUPROFEN . . .

Column/Lines	Text
Col. 1, line 1 & 2	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Col. 2, lines 20-24	. . . synergistically effective analgesic amounts of oxycodone, or a pharmaceutically suitable salt thereof, and ibuprofen, or a pharmaceutically suitable salt thereof . . .
Col. 2, line 34 & 35	. . . various dose ratios of oxycodone and ibuprofen.
Col. 2, lines 64 & 65	In a composition of the invention, oxycodone and ibuprofen are combined . . .
Col. 3, lines 23 & 24	. . . unexpectedly enhanced analgesic activity of combinations of oxycodone and ibuprofen . . .
Col. 3, lines 53-56	. . . the active ingredient is administered at a daily dosage of from about 0.05 to 7.50 milligrams per kilogram (mg/kg) of body weight of oxycodone and from about 10 to 120 mg/kg of ibuprofen.
Col. 4, lines 24-29	Example 1 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 60.0
Col. 4, lines 36-42	Example 2 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 300.0
Col. 4, lines 48-55	Example 3 Oxycodone/Ibuprofen Tablets Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 4, lines 60-66	Example 4 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 60.0
Col. 5, lines 8-14	Example 5 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 300.00
Col. 5, lines 20-26	Example 6 Oxycodone/Ibuprofen Capsules Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 5, lines 33-39	Example 7 Oxycodone/Ibuprofen Tablets Oxymorphone HCl 5.0 Ibuprofen 60.0

Column/Lines	Text
Col. 5, lines 45-51	Example 8 Oxymorphone/Ibuprofen Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 5, lines 58-63	Example 9 Oxymorphone/Ibuprofen Oxymorphone HCl 2.5 Ibuprofen 300.0
Col. 6, lines 1-7	Example 10 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 60.0
Col. 6, lines 13-19	Example 11 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 6, lines 25-31	Example 12 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 2.5 Ibuprofen 300.0
Col. 6, lines 38-43	Example 13 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 6, lines 49-55	Example 14 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 300.0
Col. 6, lines 61-66	Example 15 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 2.5 Ibuprofen 300.0
Col. 7, lines 9-14	Example 16 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 7, lines 21-27	Example 17 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 300.0
Col. 7, lines 33-39	Example 18 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 2.5 Ibuprofen 300.0

Column/Lines	Text
Col. 7, lines 46-51	Example 19 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 60.0
Col. 7, lines 57-63	Example 20 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 300.0
Col. 8, lines 1-7	Example 21 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 13-19	Example 22 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 60.0
Col. 8, lines 26-31	Example 23 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 300.0
Col. 8, lines 37-43	Example 24 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 56-58	All mice are dosed sequentially by the oral route with suspensions of ibuprofen and/or oxycodone hydrochloride solutions.
Col. 8, line 62	A stock suspension of ibuprofen is . . .
Col. 9, lines 22-24	Mice, intubated with various doses of oxycodone hydrochloride, ibuprofen, combined doses of oxycodone hydrochloride and ibuprofen . . .
Col. 9, lines 45-47	In order to study the interaction between oxycodone and ibuprofen, 5 precise dosage ratios of oxycodone hydrochloride and ibuprofen are selected.
Col. 10, lines 25 & 26	The synergistic interaction of oxycodone hydrochloride and ibuprofen . . .
Col. 10, lines 29-31	. . . the analgesic effect of oxycodone along is presented in the ordinate, and that of ibuprofen alone is on the abscissa.
Col. 10, lines 32-34	. . . exact fixed dosage ratios based on weight of oxycodone HCl:ibuprofen in the ranges of 1:1.25 to 1:31.1.
Col. 10, lines 35 & 36	. . . representing oxycodone and ibuprofen alone . . .
Col. 10, lines 36-38	. . . representing the compositions of oxycodone and ibuprofen at the fixed dosage ratios.

Column/Lines	Text
Col. 11, lines 31-33	. . . straight line additivity hypothesis for oxycodone HCl and ibuprofen . . .
Col. 12, lines 52-54	. . . analgesic synergism is established for all combinations of oxycodone and ibuprofen.
Col. 12, lines 55 & 56	By substitution of the expected analgesic activity of oxycodone alone and ibuprofen alone . . .
Col. 12, lines 62 & 63	. . . it is predicted that oxycodone and ibuprofen would demonstrate analgesic potentiation . . .
Table 1	TABLE 1 ORAL OXYCODONE HCl/IBUPROFEN COMBINATIONS Oxycodone Ibuprofen Oxycodone Ibuprofen
Col. 13, lines 49-55	1. A pharmaceutical composition comprising a synergistic analgesic combination of (a) oxycodone, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:6 to about 1:400.

As evidenced above, ibuprofen is the only NSAID mentioned throughout the entire reference, and it is the only NSAID exemplified in the Baker formulations.

g. The Examiner is improperly relying on In re Kerkhoven

The Examiner also stated in the October 5, 2006 Office Action that "the instant situation is amendable to the type of analysis set forth in *In re Kerkhoven*, wherein the court held that it is *prima facie* obvious to combine two (or more) compositions which is taught by the prior art to be useful for the same purpose. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting nabumetone for ibuprofen... "(Emphasis Added)(Citations omitted).

The fact that the Friedel and Eversmeyer references discuss the benefits of nabumetone over other NSAIDs does not provide the requisite motivation to substitute the ibuprofen of the Baker reference, when the Baker reference visibly contemplates only ibuprofen. Further, even when read in the most favorable light to use NSAIDs other than ibuprofen, a position which the Applicants do not support, the suggestion of other

NSAIDs must be interpreted in view of the teachings of the Sunshine reference, which exclude the use of nabumetone.

Therefore, Applicants respectfully submit that the Examiner's statements indicate that *In re Kerkhoven* is not being properly applied in rejecting the present claims. As stated by the Examiner, the holding of *In re Kerkhoven* is with respect to combining references. However, the Examiner's rejection, is based on modifying the Baker analgesic composition. Applicants respectfully submit that a combination of the Baker analgesic composition with nabumetone would result in a formulation including a combination of nabumetone and ibuprofen and an opioid analgesic, and therefore would not result in the presently claimed invention.

Accordingly, in view of the above, Applicants respectfully request that the rejections over the Baker, Friedel and Eversmeyer references be removed.

C. Rejection under 35 U.S.C. 103 (a) over Baker et al., Friedel et al. and Eversmeyer et al. in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)

Applicants respectfully submit that, for the reasons discussed above, the Baker reference, the Friedel reference and the Eversmeyer reference fail to teach or suggest the presently claimed method of effectively treating pain by administering a combination of two analgesic compounds and/or pharmaceutically acceptable salts thereof consisting of (i) nabumetone and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof.

Applicants further submit that the Oshlack references also fail to teach or suggest the presently claimed method of effectively treating pain by administering a combination of analgesic compounds consisting essentially of (i) nabumetone and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof.

Accordingly, as the Oshlack references fail to cure the deficiencies of the Baker Friedel and Eversmeyer references, Applicants respectfully request that the rejections over the Baker, Friedel and Eversmeyer references in view of either Oshlack references be removed.

III. CONCLUSION

In view of the foregoing, it is believed that the application is now in condition for allowance, and applicants respectfully request such action.

The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Applicants note that a Notice of Appeal was filed and received by the Patent Office on January 9, 2007. Therefore, a response is due June 9, 2007 with a three-month extension of time. As June 9, 2007 fell on a Saturday, this response is being timely filed on Monday, June 11, 2007 concurrently with a Request for Continued Examination, a Petition for a three-month extension of time and associated fees.

Respectfully submitted,
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Roxane Laboratories—Cont.

ROXICET™ Tablets Ⓒ Ⓡ
[rox-e-cet]
Oxycodone and Acetaminophen Tablets USP
(Oxycodone Hydrochloride 5 mg and Acetaminophen 325 mg)
(WARNING: May be habit forming)

ROXICET™ Oral Solution Ⓒ Ⓡ
Oxycodone and Acetaminophen Oral Solution
(Oxycodone Hydrochloride 5 mg and Acetaminophen 325 mg Oral Solution per 5 mL)
(WARNING: May be habit forming)

ROXICET 5/500™ Caplet Ⓒ Ⓡ
Oxycodone and Acetaminophen Tablets USP
(Oxycodone Hydrochloride 5 mg and Acetaminophen 500 mg)
(WARNING: May be habit forming)

DESCRIPTION

Each tablet contains:
Oxycodone Hydrochloride+ ..... 5 mg
(Warning: May Be Habit Forming)
Acetaminophen ..... 325 mg
Each 5 mL contains:
Oxycodone Hydrochloride+ ..... 5 mg
(Warning: May Be Habit Forming)
Acetaminophen ..... 325 mg
Alcohol 0.4%
Each caplet contains:
Oxycodone Hydrochloride+ ..... 5 mg
Warning: May be Habit Forming)
Acetaminophen ..... 500 mg
(+5 mg Oxycodone HCl is equivalent to 4.4815 mg Oxycodone.)

HOW SUPPLIED

ROXICET™ Tablets, Oxycodone and Acetaminophen Tablets USP (Oxycodone Hydrochloride 5 mg and Acetaminophen 325 mg) white scored tablets (Identified 54 543).
NDC 0054-8650-24: Unit dose, 25 tablets per card (reverse numbered), 4 cards per shipper.
NDC 0054-4650-25: Bottles of 100 tablets.
NDC 0054-4650-29: Bottles of 500 tablets.
ROXICET™ Oral Solution,
Oxycodone and Acetaminophen Oral Solution
(Oxycodone Hydrochloride 5 mg and Acetaminophen 325 mg Oral Solution per 5 mL)
NDC 0054-8648-16: Unit dose Patient Cups™ filled to deliver 5 mL (Oxycodone Hydrochloride 5 mg, Acetaminophen 325 mg), ten 5 mL Patient Cups™ per shelf pack, 4 shelf packs per shipper.
NDC 0054-3686-63: Bottles of 500 mL.
ROXICET 5/500™ Caplets,
Oxycodone and Acetaminophen Tablets USP
(Oxycodone Hydrochloride 5 mg and Acetaminophen 500 mg), white scored capsule-shaped tablets (Identified 54 730).
NDC 0054-8784-24: Unit dose, 25 caplets per card (reverse numbered), 4 cards per shipper.
NDC 0054-4784-25: Bottles of 100 caplets.
Store at Controlled Room Temperature (15°–30°C (59°–86°F).
DEA Order Form Required.
Caution: Federal law prohibits dispensing without prescription.

ROXICODONE™ Ⓒ Ⓡ
[rox-e-cō-dōne]
(oxycodone hydrochloride)
Tablets USP, Oral Solution USP, and Intensol™

DESCRIPTION

Each tablet contains:
Oxycodone Hydrochloride ..... 5 mg
(WARNING: May be habit forming)
Each 5 mL Oral Solution contains:
Oxycodone Hydrochloride ..... 5 mg
(WARNING: May be habit forming)
Each mL Intensol™ contains:
Oxycodone Hydrochloride ..... 20 mg
(WARNING: May be habit forming)
Inactive Ingredients:
The tablets contain microcrystalline cellulose and stearic acid.
The oral solution contains alcohol, FD&C Red No. 40, flavoring, glycol, sorbitol, water, and other ingredients.
The Intensol™ contains citric acid, sodium benzoate, and water.
Oxycodone is 14-hydroxydihydrocodeinone, a white odorless crystalline powder which is derived from the opium alkaloid, thebaine.

ACTIONS

The analgesic ingredient, oxycodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of oxycodone are analgesia and sedation.
Oxycodone is similar to codeine and methadone in that it retains at least one half of its analgesic activity when administered orally.

INDICATIONS

For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Hypersensitivity to oxycodone.

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type, and therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, this drug is subject to the Federal Controlled Substances Act.
Usage in Ambulatory Patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.
Interaction with Other Central Nervous System Depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone hydrochloride may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.
Usage In Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, this drug should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.
Usage In Children: This drug should not be administered to children.

PRECAUTIONS

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute Abdominal Conditions: The administration of this drug or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.
Special Risk Patients: This drug should be given with caution to certain patients such as the elderly, or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS

The most frequently observed adverse reactions include light headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.
Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION

The usual adult oral dose is 10 to 30 mg every 4 hours as needed for pain or as directed by physician. The dose must be individually adjusted according to severity of pain, patient response and patient size. More severe pain may require 30 mg or more every 4 hours. If the pain increases in severity, analgesia is not adequate or tolerance occurs, a gradual increase in dosage may be required.
For control of severe, chronic pain in patients with certain terminal diseases, this drug should be administered on a regularly scheduled basis, every 4 hours, at the lowest dosage level that will achieve adequate analgesia.

DRUG INTERACTIONS

The CNS depressant effects of oxycodone hydrochloride may be additive with that of other CNS depressants. See WARNINGS.

MANAGEMENT OF OVERDOSAGE

Signs and Symptoms: Serious overdose of oxycodone hydrochloride is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia. In severe overdosage, apnea, circulatory arrest and death may occur.
Treatment: Primary attention should be [illegible] tablishment of adequate respiratory exch[illegible] vision of a patent airway and the institu[illegible] controlled ventilation. The narcotic ante[illegible] specific antidote against respiratory dep[illegible] result from overdosage or unusual sensiti[illegible] including oxycodone. Therefore, an appro[illegible] oxone (usual initial adult dose: 0.4 mg) s[illegible] tered, preferably by the intravenous route[illegible] with efforts at respiratory resuscitation. Si[illegible] of action of oxycodone may exceed that of th[illegible] patient should be kept under continuous [illegible] repeated doses of the antagonist should be [illegible] needed to maintain adequate respiration. [illegible] An antagonist should not be administered [illegible] of clinically significant respiratory [illegible] depression.
Oxygen, intravenous fluids, vasopressors and [illegible] ive measures should be employed as indica[illegible] Gastric emptying may be useful in remov[illegible] drug.

HOW SUPPLIED

5 mg white scored tablets. (Identified 54 [illegible]
NDC 0054-8657-24: Unit dose, 25 tablets [illegible] numbered), 4 cards per shipper.
NDC 0054-4657-25: Bottles of 100 tablets.
5 mg per 5 mL Oral Solution.
NDC 0054-8545-16: Unit dose Patient Cu[illegible] liver 5 mL (oxycodone hydrochloride 5 mg) [illegible] Cups™ per shelf pack, 4 shelf packs per [illegible]
NDC 0054-3682-63: Bottles of 500 mL.
20 mg per mL Intensol™
(Concentrated Oral Solution)
NDC 0054-3683-44: Bottles of 30 mL with C[illegible] [graduations of 0.25 mL (5 mg), 0.5 mL (1[illegible] (15 mg), and 1 mL (20 mg) on the dropper.
DEA Order Form Required

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SODIUM POLYSTYRENE SULFONATE SUSPENSION USP

CATION-EXCHANGE RESIN

DESCRIPTION

Sodium Polystyrene Sulfonate Suspension [illegible] ministered orally or in an enema and con[illegible] per 60 mL:
Sodium Polystyrene Sulfonate USP .....
Sorbitol USP .....
Alcohol .....
The suspension is carmel-cherry-flavored [illegible] Propylene Glycol USP, Microcrystalline C[illegible] boxymethylcellulose Sodium, Methylpara[illegible] paraben NF, Saccharin Sodium USP, Fl[illegible] Water USP.
Sodium Polystyrene Sulfonate is a benzene[illegible] mer with ethenylbenzene, sulfonated, sod[illegible]
The sodium content of the suspension is [illegible] per 60 mL. It is a brown, slightly viscous [illegible] *in-vitro* exchange capacity of approximate[illegible] approximately 1 mEq) of potassium per [illegible] suspension.

CLINICAL PHARMACOLOGY

As the resin passes along the intestine or [illegible] colon after administration by enema, th[illegible] partially released and are replaced by [illegible] the most part, this action occurs in the la[illegible] excretes potassium ions to a greater de[illegible] small intestine. The efficiency of this pro[illegible] unpredictably variable. It commonly ap[illegible] of 33%, but the range is so large that defi[illegible] trolyte balance must be clearly monitor[illegible] are unavailable.

INDICATIONS AND USAGE

Sodium Polystyrene Sulfonate suspensi[illegible] treatment of hyperkalemia.

CONTRAINDICATIONS

Sodium Polystyrene Sulfonate suspensi[illegible] in patients with hypokalemia or those [illegible] persensitive to it.